PERSPECTIVE

# The New Era in Cancer Research

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For many years, discoveries about the genetic determinants of cancer appeared to be having only minor effects on efforts to control the disease in the clinic. Following advances made over the past decade, however, a description of cancer in molecular terms seems increasingly likely to improve the ways in which human cancers are detected, classified, monitored, and (especially) treated. Achieving the medical promise of this new era in cancer research will require a deeper understanding of the biology of cancer and imaginative application of new knowledge in the clinic, as well as political, social, and cultural changes.

The conquest of cancer continues to pose great challenges to medical science. The disease is notably complex, affecting nearly every tissue lineage in our bodies and arising from normal cells as a consequence of diverse mutations affecting many genes. It is also widespread and lethal; currently the second most common cause of death in the United States, it is likely to become the most common in the near future. Despite large federal and industrial investments in cancer research and a wealth of discoveries about the genetic, biochemical, and functional changes in cancer cells, cancer is commonly viewed as, at best, minimally controlled by modern medicine, especially when compared with other major diseases. Indeed, the age-adjusted mortality rate for cancer is about the same in the 21st century as it was 50 years ago, whereas the death rates for cardiac, cerebrovascular, and infectious diseases have declined by about two-thirds (1).

## A Perspective on the History of Cancer Research

The recent death of Joseph Burchenal (2), one of the pioneers in the use of chemotherapy, provides a vantage point for thinking about the history and the future of cancer research and its implications for control of the disease. Just over 50 years ago, Burchenal (Fig. 1) and his colleagues used analogs of folic acid, methotrexate, and of a nucleoside, 6-mercaptopurine, to induce profound and sustained remissions in children with aggressive leukemias (3). This event—viewed in combination with related, contemporaneous work by Sidney Farber and by Emil Frei and Emil Freireich—was revolutionary: For the first time, drugs of known chemical composition that interfered with enzymes engaged in a specific biological process, DNA replication, were used to treat cancers successfully in a rational manner. The several successful cases inspired the design of clinical trials, permitting the measurement of gradual improvements in treatment protocols. The resulting progress against childhood leukemias, despite the toxicity of the drugs and the lethality of the diseases, built confidence in the

notion that biology and chemistry could be harnessed to benefit patients with cancer (4).

At the time that Burchenal began treating leukemias, little was known about the causes of cancers or about the genetic and molecular mechanisms by which they arise from normal cells. His therapeutic strategy was based largely on the premise that cancer cells replicate their DNA and divide more frequently than most normal cells and hence would be more sensitive to DNA damage. Although this concept has proven to be an overly simplistic explanation, an emphasis on damage to DNA and the mitotic apparatus has guided the development of the many chemotherapeutic regimens and radiotherapies that have been used for nearly all types of cancers over the past 50 years. The results have ranged from modest at best (in the advanced stages of some of the most common carcinomas of adults), to partially protective against subsequent metastasis (when used as an adjuvant to surgery in the early stages of such diseases), to highly effective (in the treatment of even advanced stages of testicular cancers, some lymphomas, and a few other tumor types).

During most of those 50 years, pharmaceutical chemistry continued to serve cancer patients much more effectively than did cancer biology. Laboratory-based investigations into the nature of cancer cells and clinical efforts to control cancer often seemed to inhabit separate worlds. In the world of laboratory research, the characterization of cancer viruses of animals in the 1960s and 70s, the discovery of the first proto-oncogenes and tumor suppressor genes in the 1970s and 80s, the integration of the products of those genes into cell signaling pathways in the 1990s, and even the repeated unveilings of mutant genes implicated in human cancers beginning in the early 1980s—all seemed to have little or no impact on the methods used by clinicians to diagnose and treat cancers.

## The Rise of Molecular Oncology

During the past decade, perceptions about this situation have been changing rapidly. Understanding the genetic and biochemical mechanisms by which cancers arise and behave is now widely believed to portend improvements in the way we detect, classify, monitor, and treat these diseases. This

message has been driven home, gradually but effectively, by a variety of new and less toxic agents for treating cancers—hormones, antibodies, and enzyme-inhibitory drugs—and, especially, by the dramatic arrival of a near-miraculous drug, imatinib (Gleevec), a "molecule-specific" agent that induces nearly complete and sustained remissions in nearly all patients in the early stages of chronic myeloid leukemia (CML), by blocking a protein-tyrosine kinase activated by a well-studied chromosomal translocation (5).

These new therapies are often called "targeted." But in a sense they are not any more targeted than the conventional chemotherapies that interfere with components of the DNA replication, DNA repair, or mitotic machineries or than radiotherapies that damage DNA in a focused field. The new breeds of treatments usually have specificity for individual cancers, reflecting the particular mutations responsible for that tumor or variations in gene expression—distinctive molecular attributes that are increasingly used to subdivide cancers assigned to the same standard histopathological subtype (6, 7). These attributes include the presence or absence of receptors that bind to hormones or to derivative antagonists; the amplification or efficient expression of genes encoding cell surface proteins that are recognized by antibodies that may inhibit cancer cells (directly or through damaging toxins or isotopes); or the activation of intracellular signaling pathways by mutant proteins that are sensitive to molecule-specific drugs.

Therapeutic successes, however limited in some situations, have prompted optimism about other uses of genetic and biochemical information—to classify tumors, to detect them early and



**Fig. 1.** Joseph H. Burchenal. [Photo: courtesy of Memorial Sloan-Kettering Cancer Center]

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monitor their growth, and to devise more ingenious ways to inhibit or reverse their growth. Two broad areas of knowledge about cancer in general—and about individual cancers arising in different cell lineages—have been especially significant in this transformation of thinking about cancer:

1) The genetic basis of cancer. Mutations are now recognized to be the fundamental lesions driving neoplasia (8). The mutations are largely somatic, but sometimes hereditary; they affect proto-oncogenes, producing a dominant gain-of-function, and tumor suppressor genes, resulting in a loss of function. The Cancer Gene Census maintained by the Sanger Center of the Wellcome Trust (9) now lists over 350 genes, situated on every chromosome (except Y), that have been causally implicated in human cancer because they have been repeatedly encountered in mutant form—amplified, deleted, translocated, or damaged by missense, nonsense, or frameshift mutations—in one or more cancer types. The mutations are supplemented by epigenetic variations (methylation of DNA or modifications of histones or transcription factors) that affect gene expression (10). The mutations and the secondary changes in gene expression provide new tools for classifying tumors, for predicting their behavior, for anticipating means to detect them early, for designing new tools for imaging, and for developing therapeutic strategies. In addition, germ line mutations associated with cancers have been observed in 66 genes (9), making them candidates for assessment of genetic risks of certain cancers (11).

2) The physiology of cancer. The biological behavior of cancer cells has increasingly been linked to underlying mutations through an understanding of the signaling pathways that govern the cell cycle and cell growth, programmed cell death (apoptosis), longevity, motility, metabolism, and genome integrity. Furthermore, in addition to the physiological characteristics of cancer cells themselves, components of a cancer cell's environment are now recognized to be important for understanding cancer and considering new means to attack it. The so-called hallmarks of cancer (12) include the acquisition of self-sufficient signals for growth, the capacity for extended proliferation, resistance to growth-inhibiting signals, the ability to evade cell death signals, the potential for tissue invasion and metastasis, and the power to induce blood-vessel formation (angiogenesis). Some of these traits are the properties of the cancer cells themselves, but others depend on communication between the cancer cells and their cellular and macromolecular environments. Each property constitutes a vulnerability in a tumor, to be exploited by new therapies, especially when the underlying mutations and signaling aberrations are known.

Still, despite all this new knowledge and despite the startling success of imatinib in the treatment of CML, most of the effects of the new

era in cancer research are promised, not achieved. Classification of tumors based on analysis of DNA and RNA is still an uncertain art and practiced only in a few academic centers, largely on an experimental basis. Development of reliable new biomarkers for detection of tumors and of novel, high-affinity ligands for imaging, based on evidence of changes in the structure or production of certain proteins in specific cancers, has yet to occur. The impact of the new generation of molecularly targeted therapies on overall cancer mortality rates remains negligible, because imatinib is effective only in CML and a few other relatively uncommon cancers; because other tyrosine kinase inhibitors dramatically shrink only those lung cancers with mutations in the epidermal growth factor receptor (13), and the impact on survival in this group of patients has yet to be established in prospective studies; and because antibodies against cell surface proteins that are effective as adjuvant therapies, such as anti-HER2 in early breast cancer (14, 15), have not yet been used long and widely enough to affect public health data.

## Oncogene Dependence

So why is there so much excitement about new cancer therapies? One reason is based on an unexpected consequence of interfering with activated oncogenes. The remarkable reduction in the number of cancer cells observed after treatment with imatinib and some other tyrosine kinase inhibitors implies that such drugs do not simply arrest tumor cell proliferation when they block oncogene activity; they eliminate tumor cells, most likely by programmed cell death. The idea that cancer cells are dependent on mutant oncogenes for viability, not just growth—often called "oncogene dependence" (16) or "oncogene addiction" (17)—is also supported by studies of cancer cell lines and animals. In mice carrying oncogenes as transgenes that can be regulated by transcriptional control, a wide variety of tumor types swiftly regress, mainly by apoptosis, when the oncogenic proteins are de-induced (16, 18).

The concept of oncogene dependence encourages efforts to destroy cancer cells with new therapeutics directed specifically against the products of mutant oncogenes, but it is still a poorly understood phenomenon. At its heart is a vexing question: How did a cell that was originally content without an oncogene become ready to die if deprived of it? Answers to this question could guide strategies for exploiting a cancer cell's dependence on some of the most frequently encountered oncogenes, such as members of the RAS and MYC gene families, for which therapeutic agents are currently lacking. This will entail learning more about the vulnerabilities of cells dependent on oncogenic proteins that do not function as enzymes (e.g., Myc and other oncogenic transcription factors) or those that have lost a catalytic activity (e.g., mutant Ras proteins lacking guanosine triphosphatase activity).

Several other issues require attention before oncogene dependence can be adequately exploited for diagnostic and therapeutic purposes:

1) The mutational repertoire. Most obviously, the catalog of oncogenic mutations associated with the many forms of human cancer is far from complete. The Cancer Genome Atlas (TCGA) initiative, recently announced by the National Institutes of Health (NIH) (19), should substantially improve this situation over the next decade. The high-throughput technologies that make this initiative possible can, in principle, be used to survey sets of hundreds of tumors, each set representing one of the common malignancies, for determination of gene copy number, gene expression pattern, and sequences of the exons of 1000 to 2000 genes (20). Development of new methods for DNA sequencing (21) could appreciably drive down costs of TCGA, and faster methods for karyotyping could extend the project to detect chromosomal rearrangements, which are proving to be very common mechanisms of oncogenic mutation (9). TCGA is intended to assist the development of therapeutic strategies, but the portraits of molecular changes in many cancer types should also offer new ideas about diagnosing and classifying cancers, detecting them earlier with biomarkers, and monitoring them during therapy with novel imaging methods.

2) Mutational hierarchies. Most if not all tumors have multiple mutations affecting known cancer genes, but the relative importance of such mutant genes in maintaining the oncogenicity and viability of a cancer cell is not known. The loss of responsiveness to anti-HER2 antibody after a tumor suppressor gene (PTEN) is mutated in human breast cancers (22), and loss of dependence on the c-Myc oncogene in mouse breast tumors when a mutation occurs in another oncogene (Ras) (23), imply that therapies addressing multiple genetic changes will be required. On the other hand, in some genetically engineered mice, oncogene dependence is not affected by the coexistence of an oncogenic mutation in another gene (24). Experiments that explore the hierarchy of mutations in different types of tumors could guide the selection of the most appropriate molecular targets and the design of multi-agent therapies.

3) Secondary resistance. All targeted therapies are limited by the appearance of resistance to drugs or antibodies. In some highly instructive cases, resistance can be attributed to a limited repertoire of secondary mutations in targets such as oncogenic tyrosine kinases (25, 26), providing a basis for screening for drug resistance and for seeking new agents that can prevent or overcome it. Deciphering mechanisms of resistance and developing multi-agent treatment protocols, resembling the anti-HIV combination therapies that reduce the likelihood that drug resistance will emerge, will be essential to achieve long-term control of cancers.

4) Heterogeneity and stem cells. The use of differentiation markers reveals heterogeneity among neoplastic cells in a single tumor (27, 28). Some if not all tumors are thought to contain a minor population of cells (so-called cancer stem cells) that are responsible for the tumor's continued expansion and for its regeneration when once-effective therapies fail (29, 30). Better characterization of cancer stem cells and the means to isolate them may help to monitor this subset of cells during treatment and to design treatments that selectively kill them, thereby eliminating a tumor's potential for regrowth.

This list is, of course, incomplete. It remains to be established, for example, whether all cancers show oncogene dependence; whether there is a relationship between oncogene dependence and metastatic potential; and whether components of signaling mechanisms "downstream" of mutant oncogenic proteins (31) can commonly serve as targets for therapeutic intervention.

## Attacking Cancer Cells Indirectly

An enlarged understanding of the tissue environment in which cancers grow is providing new opportunities to develop therapies that are not targeted at the tumor cells themselves. Best known among these novel approaches is the anti-angiogenic strategy, for which drugs and antibodies have already been approved by the Food and Drug Administration (FDA) (32).

There are grounds for optimism about other approaches that address the tumor's milieu: (i) by interfering with growth-promoting signals supplied by non-neoplastic "stromal cells" that surround a tumor (33); (ii) by inhibiting specific proteases that mold a tumor's environs to promote the dangerous escape of tumor cells into the circulation (34, 35) or by using those proteases to activate molecules useful for imaging tumors (36); and (iii) by promoting an immune response against tumor cells—for example, by inactivating factors, such as the T cell surface protein CTLA-4 (37), that restrict the immune response to cancer cells.

## Placing Selective Therapies in Perspective

Despite these encouraging ideas, enthusiasm for harnessing new knowledge to combat cancer clinically can seem naïvely overpromising; simplistic about the medical and social attributes of cancer; unperceptive about the history of incorporating complex technical changes into the general practice of medicine; and neglectful of the many other ways cancer can be controlled. Surgery, chemotherapy, radiation, histopathology, and conventional imaging are likely to remain the staples of cancer care for many years. And they too are becoming more effective, even without any molecular advances, through image-guided and minimally invasive surgery, positron emission tomography–computed tomography scanning, dose-modulated radiotherapy, and other technologies.

Other means to control cancer have also been developed, improved, or more widely used in recent years. These include strategies for prevention [such as smoking cessation programs, vaccines against cancer-promoting viruses (hepatitis B and papilloma viruses), and methods for detection of premalignant lesions and early cancers (e.g., colonoscopies, mammography, and PAP smears)]; neurotropic medications to control the ancillary symptoms of cancer, most obviously pain and nausea; hematopoietic growth factors to blunt the side-effects of cytotoxic treatments, such as anemia and leukopenia; and psychosocial methods for managing the response of patients and families to the diagnosis and treatment of cancers.

Furthermore, as a recent inventory of U.S. cancer rates and trends makes evident (38), successful control of cancer will require more than just new technologies, whether molecularly based or not. It also calls for elimination of disparities in care—and in access to care—that are based on racial and economic factors.

## Gauging the Future

It is difficult to appraise the progress that has been made against cancer over the past half-century, but even more so to predict the progress that should be anticipated over the next 10 or 50 years, because cancer is such a complex problem, with hundreds of forms, diverse means of controlling it, and daunting social barriers to reducing its burdens. To argue that the fight against cancer has been disappointing, one can simply recall that age-adjusted mortality rates now are about the same as they were 50 years ago. But it is also legitimate to support a more optimistic view by noting the recent annual 1% declines in mortality rates after several decades of steady increases (38); the enormous improvements in treatments of a few adult and several pediatric cancers; the large increases in 5-year patient survival rates for many cancers (39); the recent development and FDA approval of several narrowly targeted therapies with mild side-effects; and the several ways in which living with advanced cancer has been made better by controlling the symptoms of even resilient underlying disease.

Regardless of how the current situation is viewed, the United States and many other countries are faced with a daunting demographic reality: With the continued aging of the population, the absolute number of cancer diagnoses will very likely rise substantially in the coming decades. So, for the foreseeable future, we will need better ways to detect and treat cancers, especially the solid tumors of the lung, breast, prostate, colon, pancreas, ovary, and other organs that are common in older age groups. Articles in this issue provide grounds for optimism about the prospects for better means to control such cancers if new research opportunities are fully exploited. But science operates in a cultural context that affects the deployment of the limited financial resources and human talent devoted to cancer. From that perspective, there is a great deal to worry about.

The major public support for cancer research in the United States comes from the National Cancer Institute (NCI) and, to lesser degrees, from several other components of the NIH. Despite a much welcomed doubling of the NIH budget from 1998 to 2003, appropriations to the NCI specifically, and to the NIH generally, have not kept pace with inflation since then (40). As a result, the buying power of the NIH has been substantially eroded, and the success rates for grant applications have fallen to discouraging levels. In this atmosphere, it is difficult to take on new and expensive projects and to attract the best young talent even to this exciting and important area of research. Furthermore, the leadership of the nation's cancer efforts has been poorly defined in recent months and will remain so until a new NCI director is appointed (41, 42).

Traditionally, the public has looked to the pharmaceutical and biotechnology industries for new tools to detect and treat a wide spectrum of diseases, based largely on the results of publicly funded basic science. But a number of factors raise questions about how, in oncology, this tradition may be challenged by a future increasingly influenced by a molecular view of cancer. Will industry lose incentives to develop targeted therapies that address small, precisely defined classes of tumors? Or will commonalities among tumors, such as the high frequency of mutations in RAS genes (43), sustain market sizes? Will the high prices of some recently approved cancer therapies (44) be sustainable, given increasing pressures on health care financing? Will government agencies and private insurers continue to provide adequate reimbursement for molecular methods for detecting, diagnosing, and monitoring tumors as the use of these currently expensive technologies expands? Will regulatory agencies and industry find common ground to allow affordable and interpretable clinical trials for drugs for uncommon cancers, perhaps by using early indicators of therapeutic success, such as biomarkers in serum? And will companies collaborate to test multi-agent therapies directed at multiple targets?

Finally, the new era in cancer research calls for changes in the culture of oncology. These include stronger working relationships between bench scientists and their clinical colleagues, between oncologists in academia and those in community hospitals, and between oncologists and other physicians; new training programs that provide graduate students in the basic sciences with an opportunity to understand the dilemmas posed by cancer as a human disease; grant mechanisms and criteria for advancement in academia that support the kind of teamwork traditionally associated with industry; and guarantees of access to the molecular data sets generated with public funding, to enhance their usefulness for investigators, practitioners, and patients and their advocates.

In sum, concerted national efforts to ensure the vitality of all of the components of modern oncology—academic research, industrial development, and the delivery of new methods throughout the health care arena—are essential to an optimistic view of the prospects for transforming an understanding of oncogenic mechanisms into therapeutic benefits for our entire society.

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